REMARKS

Claims 52-68 are pending. Rejections are levied under 35 U.S.C. Section 112, first paragraph (written description), Section 112, first paragraph (enablement), Section 112, second paragraph(indefiniteness), Section 102, and Section 103. Applicants note that the Examiner did not state that the outstanding rejections of claims 34, 35, 43, 44, 49 and 50 under Section 112, first paragraph (written description and enablement) were withdrawn, but did not relevy these rejections. Thus, these rejections do not apply to the claims 52-68 as pending before entry of this amendment. By this amendment, claims 52-68 are canceled without prejudice or disclaimer. New claims 69-78 are added. New claims 69-78 are provided to clarify the invention and are not in response to the previously levied rejections under Section 112, paragraph 1 (enablement and written description).

Support for new claim 69 is found throughout the specification, including page 3, lines 6-9; page 17, lines 20-35; Example V ("lymphoid or hematopoietic"); page 6, lines 20-26; page 8, lines 8-10; page 11, lines 7-11; page 17, lines 20-34; page 19, line 14 to page 23, line 30; and in original claim 1, and previously pending claims 31 and 52. Applicants note that "non-tumor" lymphoid or hematopoietic cells is implicitly disclosed by the cells exemplified in Example V of the specification (see page 42 et seq), which describes bone marrow progenitor cells obtained from Balb/c mice. Support for new claims 70-72 is found throughout the specification at, for example, page 16, lines 18-22; page 17, lines 4-6; Example IV, in original claim 1 and in previously pending claims 41-47 (see also support for previously pending claims 56-58). Support for new claim 59 is found throughout the specification and in previously pending claims 37 and 59. Support for new claim 74 is found throughout the specification, for example, at page 12, lines 28-32; page 16, lines 18-22; page 17, lines 4-6; Example 4; in original claims 1 and 3, and in previously pending claims 32, 41, 47, and 61. Support for new claim 75 is found throughout the specification, for example, in Examples IV and V. Support for new claim 76 is found throughout the specification, for example, on page 17, lines 20-34; page 19, line 14 to

page 23, line 30, and in pending claim 66. Support for new claims 77 and 78 is found throughout the specification, for example, at page 17, line 26 and line 30; Example V; and in previously pending claim 40.

Applicants note that the submission filed on September 21, 2001 (Paper No. 28) and the Declaration of Dr. David W. Scott have been entered.

Attached hereto is a marked up version of the changes made to the specification by the current amendment with additions underlined and deletions bracketed. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Examiner Interview

Applicants wish to thank the Examiner and his supervisor for the courtesy of granting an interview to Applicants' representatives on April 17, 2002 during which interview the pending rejections were discussed. The results of the interview are reflected in this response.

Specification formalities

Sequence listing

Applicants note that a new sequence listing is enclosed herewith, in response to the Examiner's objections. With respect to the Examiner's comment on the sequence on page 31, Applicants note that the sequence is a single double stranded sequence corresponding to SEQ ID NO:1, and that the sequence listing for SEQ ID NO:1 states that the sequence is double stranded.

Applicants believe that this clearly indicates that the sequence shown on page 31 represents a single, double-stranded DNA molecule. However, to address he Examiner' concern, Applicants have additionally listed the second strand as SEQ ID NO:11, and amended the specification to indicate that the lower sequence strand is listed in SEQ ID NO:11 and the upper sequence strand is listed in SEQ ID NO:1.

With respect to the sequence shown on page 35, the specification has been amended to clarify that the amino acid sequence corresponds to SEQ ID NO:5 and the nucleic acid sequence corresponds to SEQ ID NO:2. Applicants believe that this addresses the Examiner's concern that there are two sequences shown on page 35, but only one sequence listing.

With respect to the sequence in Figure 1, the specification has been amended to insert SEQ ID NOs corresponding to the amino acid and nucleic acid sequences shown in Figure 1. For the Examiner's convenience, a copy of the formal drawing of Figure 1 (obtained from the parent patent, U.S. Patent No. 5,817,308) is enclosed herewith. The formal drawing shows the amino acid and nucleic acid sequences more clearly. Applicants believe that this addresses the Examiner's concern that the sequences in Figure 1 do not have a description of the SEQ ID NOs.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claim 60

Claim 60 is rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification. Office Action, page 3.

Applicants respectfully direct the Examiner's attention to the parent of the present application, issued as U.S. Patent No. 5,817,308, wherein ATCC Accession No. 69555 is listed. *See* col. 9, lines 1-10. Applicants believe that this is sufficient evidence that the ATCC Number submitted previously in this case corresponds to the recited bacterial strain, and that the ATCC Number is not new matter. However, claim 60 has been canceled and new claims do not recite the ATCC Accession Number. Thus, withdrawal of this rejection is respectfully requested.

Claims 65 and 66

Claims 65 and 66 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification. Applicants note that claims 65 and 66 are cancelled. Applicants will address the rejection in the context of new claims 69-78, to the extent that it may be deemed applicable thereto. Applicants respectfully traverse this rejection for the following reasons.

The legal standard for the written description requirement

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonable conclude that the inventor had possession of the claimed invention. MPEP Section 2163.I. The Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the claimed invention is present in the specification as filed. MPEP 2162.II.A.

For reasons described in detail below, Applicants were in possession of the claimed invention at the time the application was filed.

Methods for making and delivering transformed cells were deemed described in the parent patent application

First, the parent application, issued as U.S. Patent No. 5,817,308, claims a method comprising administering transformed cells which stably produce fusion immunoglobulin molecules. *See, e.g.,* claim 21. Thus, it is evident that methods for making and administering such cells were deemed properly described in the parent case.

Pharmaceutical compositions comprising non-tumor lymphoid or hematopoietic cells are described and exemplified

Further, the specification extensively describes the claimed pharmaceutical composition that induces tolerance to an antigen, said tolerogenic composition comprising a lymphoid or

hematopoietic cell suitable for introduction into an individual and a pharmaceutically acceptable excipient as described herein.

For example, the specification states:

> Hematopoietic or lymphoid cells are stably transformed with a vector to provide transformed cells expressing the fusion immunoglobulin (Specification at page 3, lines 6-9),

and that

> [T]ransformed cells can also be introduced into animals for induction and maintenance of tolerance to the heterologous epitope expressed by the transformed cells or to an antigen containing the heterologous epitope (Specification at page 17, lines 20-23).

In addition, Example V describes preparation of bone marrow cells transfected with the vector MBAE 12-26 coding for the lambda cI 12-26 epitope, and intravenous administration into mice of a pharmaceutical composition comprising the transformed bone marrow cells suspended in HEPES buffered Eaglis medium. *See* specification at pages 42-43. Applicants note that the bone marrow cells described therein are non-tumor lymphoid cell, including cells of B cell lineage.

Suitable cells are described, including lymphoid cells and B cells, and preparation of transformed cells is described

The specification further describes, for example, transformed cells that can be introduced into animals for induction of tolerance, and lists suitable cells for transformation, including lymphoid or hematopoietic cells and cell of B cell lineage (see, e.g., page 17, lines 20-35; see also page 30, lines 6-7 (describing that "suitable transformed cells include bone marrow cells and lymphoid cells from mice or humans").

Expression cassettes, vectors, and suitable allergens are described

As noted in the last response, expression cassettes and vectors are extensively described (see, e.g., pages 8-16), including an thorough description of suitable antigens including allergens

and autoantigens (see, e.g., page 10, line 21 to page 13, line 2). Applicants point out that the specification teaches that either one epitope of an antigen can be expressed in a fusion polypeptide or alternatively, an entire antigen can be expressed in a fusion polypeptide. For example, the specification states at page 11, lines 11-34:

> [I]f tolerance is desired to a large and complex antigen, more than one epitope can be selected to be combined in a fusion immunoglobulin. Preferably, the entire antigen may be included in the fusion immunoglobulin [lines 16-20]. . . . [I]f there is little or no information known about epitopes of the antigen, it may be desirable to include the entire antigen in the fusion immunoglobulin [lines 30-34].

The specification also fully describes introduction of a vector encoding a fusion protein into suitable non-tumor lymphoid or hematopoietic cells (see, e.g., Example IV at pages 40-41; 18, lines 3-8), pharmaceutical compositions (see, e.g., page 19, line 14 - page 23 line 30), and methods of transfecting cell with expression vectors and administering the cells to animals (see, e.g., page 28, line 25 to page 30, line 15).

The Declarations of Dr. David W. Scott are submitted to show that the invention is enabled, and are discussed below with respect to the enablement rejection

Applicants respectfully point out that the Second Declaration of Dr. David W. Scott is provided to demonstrate that the invention works, and is further discussed below in the context of the enablement rejection. This declaration describes in detail additional experiments according to the teachings of the specification.

Accordingly, it is evident that Applicants have fully described the claimed pharmaceutical composition, and have provided much more than the description of "a composition solely by its principle biological function (i.e. inducing tolerance to an antigen)", as

asserted by the Examiner in the Office Action.[1] Office Action at page 4. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 65 and 66 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Applicants note that claims 65 and 66 are cancelled. Applicants will address the rejection in the context of new claims 69-78, to the extent that it may be deemed applicable thereto. Applicants respectfully traverse this rejection.

Legal standard for enablement

To satisfy the enablement requirement, the specification must provide sufficient guidance regarding how to make and use the invention to allow the ordinarily skilled artisan to carry out the invention without undue experimentation. The law is clear that a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as satisfying the enablement requirement unless there is reason to doubt the objective truth of the teachings of the specification. *In re Marzocchi*, 169 USPQ 367,369 (CCPA 1971). It is incumbent upon the Examiner to explain why one skilled in the art would doubt the truth of statements made in the specification, and provide back up assertions with acceptable and specific evidence. *Id.* at 370. Absent evidence to the contrary, the specification must be assumed to be enabling. Applicants can provide a declaration after the filing date which demonstrates that the claimed invention works. *See* MPEP § 2164.05(a).

For reasons discussed in detail below, Applicants submit that the instant specification meets the enablement requirement.

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[1] Applicants note that the instant situation is clearly different from the fact pattern of the *Eli Lilly* and *Fiers* cases cited by the Examiner, in which the applicants were claiming a previously unknown nucleotide sequence and yet the specification failed to disclose the nucleotide sequence.

Methods for making and delivering transformed cells were deemed enabled in the parent patent application

First, Applicants point out that the parent application, issued as U.S. Patent No. 5,817,308, claims a method comprising administering transformed cells which stably produce fusion immunoglobulin molecules. *See, e.g.,* claim 21. Thus, it is evident that methods for making and delivering such cells were deemed properly enabled in the parent case.

The specification teaches how to make and use the claimed invention

Moreover, the specification extensively teaches how to make and use the claimed invention. As noted in the last response, the specification describes how to prepare expression cassettes for the fusion proteins (e.g., pages 8-17). The specification further describe how to transform cells with the expression cassettes (e.g., pages 17-19), and describes suitable cells for the methods of the invention including lymphoid or hematopoietic cells, including cells of B cell lineage (see, e.g., page 17, lines 20-35; Example V). Exemplary antigenic polypeptides (including autoantigens and allergens) are described (see, e.g., page 10, line 21 to page 13, line 2), and the specification further teaches that the nucleotide sequences for antigens are available in the art and can be identified by searching in a database such as GenBank (e.g., page 10, lines 5-20). Furthermore, the specification describes how to select epitopes of the antigens, if desired, for inclusion in the fusion protein (see specification at page 11, lines 11-34, which describes the selection process for the epitopes). The specification states, for example, that

> if tolerance is desired to a large and complex antigen, more than one epitope can be selected to be combined in a fusion immunoglobulin. Preferably, the entire antigen may be included in the fusion immunoglobulin [lines 16-20]. . . . [I]f there is little or no information known about epitopes of the antigen, it may be desirable to include the entire antigen in the fusion immunoglobulin [lines 30-34].

The specification further describes pharmaceutical compositions (see, e.g., page 19, line 14 to page 23, line 30), as well as methods of transfecting cell with expression vectors and administering the cells to animals (see, e.g., page 28, line 25 to page 30, line 15).

Working examples demonstrate preparation of vectors encoding fusion polypeptides, cells transfected with the vectors, and administration of a pharmaceutical composition comprising cells to mice

Applicants note that working examples are provided demonstrating preparation of a vector comprising a fusion polypeptide, vector MBAE 12-26 coding for the lambda cI 12-26 epitope (see, e.g., Example IV), preparation of non-tumor bone marrow cells transfected with that vector, and intravenous administration into mice of a pharmaceutical composition comprising the transformed bone marrow cells suspended in HEPES buffered Eagles medium. *See* Example V, specification at pages 42-43. The bone marrow cells described therein are non-tumor lymphoid cell, including cells of B cell lineage.

The Declarations of Dr. David W. Scott describes additional experiments according to the teachings of the specification, and should be considered

Subsequent to the filing of the instant application, Applicants conducted additional experiments according to the teachings of the specification. Briefly, Applicants prepared pharmaceutical compositions comprising non-tumor lymphoid cell expressing six additional different fusion polypeptides, and tested their ability to induce tolerance when administered to a host individual.

These experiments are described in the Second Declaration of Dr. David W. Scott, submitted herewith, as well as in the Declaration of Dr. David W. Scott submitted with the last response (filed September 10, 2001).

- *Six fusion protein constructs were prepared*

Four of these fusion constructs used full-length proteins as the antigenic polypeptide incorporated into the fusion protein. The four full-length polypeptides tested were: myelin basic

protein (MBP), glutamic acid decarboxylase (GAD), lambda repressor cI protein and ovalbumin (OVA). Two other fusion constructs used subregions of antigenic polypeptides, wherein these subregions were established in the art to elicit an autoimmune response in an appropriate host. These two additional constructs tested were: interreceptor retinal binding protein (IRBP) residues 161-180 and insulin B chain residues 9-23.

- *Fusion constructs were introduced into lymphoid cells, and a pharmaceutical composition comprising these cells was administered into mice*

As further described in the Declaration, the fusion constructs were introduced into non-tumor lymphoid cells (specifically, B-cells), the lymphoid cells comprising the fusion constructs were suspended in a pharmaceutically acceptable excipient, introduced into an animal host using art-recognized model systems, and induction of tolerance was tested.

- *Induction of tolerance was demonstrated*

As explained in greater detail in the Declaration, administration of pharmaceutical compositions comprising non-tumor lymphoid cells expressing six fusion polypeptides comprising expression (fusion) constructs resulted in tolerance induction to the antigenic polypeptides incorporated into the fusion protein in a host individual.[2] Applicants submit that the Declaration in combination with the specification indicate that the present claims are broadly enabled. Withdrawal of this rejection is respectfully requested.

The Declaration should be considered because it uses the guidance of the specification coupled with art-recognized model systems

Applicants note that the Examiner in the Office Action did not consider the first Declaration of Dr. David W. Scott (submitted September 10, 2001) on the ground that "the

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[2] As discussed in the first Declaration of Dr. Scott, filed September 10, 2001, these results further demonstrate that incorporation of a full-length antigenic polypeptide or a portion thereof into a fusion protein in accordance with the teachings of the specification is sufficient to induce tolerance to a wide variety of different antigens.

declaration does not correlate to the specification as originally filed and is not adequate to enable the claims". Applicants disagree that either Declaration of Dr. David W. Scott is inadequate and request consideration of both Declarations of Dr. David W. Scott for the following reasons.

- *Legal standard for introduction of evidence relating to enablement*

Applicants can provide a declaration after the filing date which demonstrates that the claimed invention works. *See* MPEP § 2164.05(a). Further, MPEP § 2164.05(a) states that "the steps, material and conditions used in the experiments of the declaration should be compared with those disclosed in the specification to make sure that they are commensurate in scope, i.e., that the experiments used the guidance in the specification as filed as well as what was well known to one of skill in the art.").

- *The Declaration correlates to the specification*

Applicants submit that the experiments discussed in the Declaration use the guidance taught in the specification, in combination with art-recognized model systems for the study of autoimmune disease and/or allergic reaction.

- *Both the Declaration and specification describe preparation of fusion proteins, cell comprising the fusion* proteins *and administration of a pharmaceutical composition comprising the cells*

For example, the specification and the Declaration describe preparation of fusion constructs comprising polynucleotides encoding antigenic polypeptides (including autoantigens and allergens); introduction of these constructs into non-tumor lymphoid cells (which include B cells); and introduction into an animal of a pharmaceutical composition for inducing tolerance comprising (a) non-tumor lymphoid cells expressing a fusion polypeptide and (b) a pharmaceutically acceptable excipient.

- *Antigens, lymphoid or hematopoietic cells (including B cells), and administration of pharmaceutical* composition *are described in the specification*

Applicants point out that the specification specifically describes myelin basic protein at page 10, line 27 (as well as other antigenic polypeptides); transduced B cells at page 41, line 13 (*see also* page 17, lines 24-31, discussing lymphoid and hematopoietic cells, and cells of B-cell lineage, and Example V, exemplifying non-tumor lymphoid cells); and administration of a pharmaceutical composition comprising a non-tumor lyphoid cell comprising a fusion polypeptide, and a pharmaceutically acceptable excipient at, for example, Example V (pages 42-43).[3]

In response to the Examiner's statement in the Office Action that ovalbumin and lambda c1 protein are not antigens as described in the (then-pending) claims, Applicants note that ovalbumin is an egg protein, and is considered to be an allergen. Applicants also note that, as discussed at the interview, the immunological properties of the lambda c1 epitope have been extensively studied, and as such, it is an art-recognized model antigen. As such, Applicants submit that the experiments pertaining to ovalbumin and lambda protein should be considered.

- *It is not necessary for the art-recognized model systems to be disclosed in the specification in order for the Declaration to be considered*

Applicants further note that during the interview, the Primary Examiner confirmed that disclosure of allergic encephalitis (EAE) mice in the specification was not necessary in order for the Declaration to be considered.

Accordingly, it is evident that the Declaration of Dr. David W. Scott correlates with the specification as filed, and Applicants respectfully request that both Declarations of Dr. David W. Scott be considered.

In summary, Applicants submit that the present claims are fully enabled for the reasons stated above. Withdrawal of this rejection is respectfully requested.

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[3] Applicants further note that the presently pending claims do not recite the terms "mammalian antigens, autoantigens or allergenic antigens".

Rejections under 35 U.S.C. § 112, second paragraph (indefiniteness)

Claims 52-68 are rejected under 35 USC Section 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 52-54 are rejected as allegedly indefinite for reciting the phrase "polypeptide or portion thereof containing at least one epitope". Specifically, it is allegedly unclear whether "containing at least one epitope" refers to just the portion thereof or to the polypeptide and the "portion thereof". Applicants respectfully traverse this rejection.

Applicants respectfully submit that the meaning of this phrase is clear, and that one skilled in the art would understand that "containing at least one epitope" refers to the polypeptide and the "portion thereof". Applicants further point out that a search of issued patents from 1996-2002 revealed at least 40 issued patents reciting this phrase. However, claims 52-54 have been canceled and the new claims do not recite that phrase "polypeptide or portion thereof containing at least one epitope". Thus, withdrawal of this rejection is respectfully requested.

2. Claim 55 is rejected as allegedly indefinite for reciting "polypeptide, or portion thereof, of an allergen comprising at least two epitopes". Specifically, it is allegedly unclear if the phrase "comprising at least two epitopes" in the phrase refers to just the polypeptide or to the polypeptide and the "portion thereof".

Applicants respectfully submit that the meaning of this phrase is clear. Applicants further point out that a search of issued patents from 1996-2002 revealed at least 40 issued patents reciting the phrase "polypeptide or portion thereof". However, claim 55 has been canceled and the new claims do not recite that phrase "polypeptide, or portion thereof, of an allergen comprising at least two epitopes". Thus, withdrawal of this rejection is respectfully requested.

3. Claim 52 is rejected as allegedly indefinite because the scope of the term "protein" in clause 2 is allegedly unclear. Specifically, it is allegedly unclear whether the protein has one or

two epitopes" because it is unclear whether "comprising at least two epitopes" relates to just allergen protein or to mammalian proteins, autoantigenic proteins and allergen proteins.

Applicants respectfully submit that the meaning of this phrase is clear. However, claim 52 has been canceled and the new claims do not recite the offending phrase. Withdrawal of this rejection is respectfully requested.

4. Claim 52 is rejected as allegedly indefinite because using "mammalian antigenic polypeptide" and "autoantigenic polypeptide" in the same Markush group is allegedly indefinite. Specifically, it is allegedly unclear "whether Applicants believe these to be separate terms or if there is overlap." The Office Action also states that the terms are not defined in the specification and are relative terms that would have various meanings in the art. Applicants respectfully traverse this claims.

Applicants respectfully submit that the use of the terms "mammalian antigenic polypeptide" and "autoantigenic polypeptide" in the same Markush group is not a ground for a rejection under Section 112, second paragraph. According to MPEP Section 2172.05(h), the presence of allegedly overlapping terms in a Markush group is generally not sufficient basis for objection or rejection of the claims. For example, the MPEP provides that the following Markush group is acceptable" "a group including amino, halogen, nitro, chloro and aklyl, even though halo encompasses chloro". Accordingly, it is evident that Markush groups with allegedly overlapping members are not contrary to the law, even when one Markush group member completely overlaps with another Markush group member, as in the example cited in MPEP Section 2172.05(h). Applicants submit that the present claims are similarly acceptable.

However, as noted above, claim 52 has been canceled, and the new claims do not recite the terms "mammalian antigenic polypeptide" and "autoantigenic polypeptide" in the same Markush group. Withdrawal of this rejection is respectfully requested.

5. Claims "reciting mammalian antigenic polypeptide" are rejected as allegedly indefinite. Specifically, it is allegedly unclear whether the phrase is intended to mean

"mammalian polypeptides that are antigenic or polypeptides that are antigenic in mammals. The latter would allegedly include viral proteins, pollen, etc." Applicants note that claims 52 and 53 recite this phrase.[4] Applicants respectfully traverse this rejection.

Applicants respectfully submit that the meaning of this phrase is clear and that one of ordinary skill would understand the phrase to mean mammalian polypeptides that are antigenic. However, as noted above, claims 52 and 53 have been canceled and the new claims do not recite this phrase. Withdrawal of this rejection is respectfully requested.

6. Claims 52, 54, and 62 are rejected as allegedly indefinite for reciting the term "autoantigenic". The Examiner states that Applicants' argument (made in the last response) that the term has an art-recognized meaning because the term "autoantigenic" describes proteins relative to their host. Thus, it is allegedly unclear "if the term refers only to protein isolated from a host having an autoimmune response against that protein or if it can it[sic] also be isolated from a healthy individual."

Applicants respectfully disagree with the Examiner for the reasons stated in the last response. However, claims 52, 54, and 62 have been canceled and the new claims do not recite the term "autoantigen". Withdrawal of this rejection is respectfully requested.

7. Claim 58 is rejected as allegedly indefinite because "it is unclear if the claim encompasses two copies of the vector or if the vector comprises two copies of the nucleic acid sequence encoding the fusion protein." It is allegedly unclear if the two copies are operably linked to one promoter or if each copy is operably linked to a promoter. Office Action, page 8.

Applicants note that claim 58 has been canceled. Applicants will address this rejection in the context of new claim 72, to the extent that the rejection is deemed to apply to this claim.

As a preliminary matter, Applicants note that the Examiner suggested the phrase "encoding at least two fusion proteins operatively linked to a promoter" in the interview held April 17, 2001. Applicant respectfully submit that the present language of claim 58, "two or

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[4] The Office Action did not list the claims that were rejected.

more copies of the nucleic acid sequence encoding said fusion protein operatively linked to said promoter", is similar to the language proposed by the Examiner.

Applicants further respectfully submit that claim 72 is clear. Applicants note that claim 72 does not recite two copies of the vector, as suggested by the Examiner, but rather recites "two or more copies of the nucleic acid sequence encoding said fusion protein operatively linked to said promoter". Applicants respectfully submit that it is clear that claim 72 refers to two copies of the nucleic acid sequence encoding the fusion protein operatively linked to a promoter. Withdrawal of this rejection is respectfully requested.

8. Claim 60 is allegedly indefinite for reciting the term "characteristics". It is allegedly unclear whether applicants intend to claim a physical characteristic or a function.

Applicants disagree that the term "characteristics" render claim 58 indefinite. However, claim 58 has been canceled and the pending claims do not recite the term "characteristics". Withdrawal of this rejection is respectfully requested.

9. Claim 62 is rejected as allegedly indefinite for reciting the term "histocompatability antigen". It is allegedly unclear "whether applicants intend to claim a particular epitope derived from a histocompatability molecule such as B7 or whether applicants intend to claim an epitope derived from a protein involved in histocompatability such as antibodies involved in tolerance."

Applicants disagree that the term "histocompatability antigen" is unclear. As described above, the term "autoantigen" has an art-established meaning. In the context of an autoantigen, the meaning of the term "histocompatibility antigen" would also be known to the person of skill in the art, and thus is not indefinite. However, claim 62 has been canceled and the pending claims do not recite the term "histocompatability antigen". Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

Zanetti

Claims 52-55, 58 and 65-68 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Zanetti (U.S. Patent No. 5,508,386, April 16, 1996)[5]. Zanetti is cited as teaching a fusion vector encoding a fusion protein comprising an immunoglobulin and an antigen and J588 cells transfected with the vector. *See* Office Action at 9. Applicants respectfully traverse this rejection.

Applicants note that claims 52-68 have been canceled. Applicants will address the rejection in the context of pending claims 69-78, to the extent that the rejection may be deemed to so apply.

The Examiner has not made a prima facie case of anticipation

For a cited reference to anticipate a claimed invention, the reference must disclose each and every element of the claimed invention. The Examiner has not made a *prima facie* case that Zanetti anticipates the claims as presently pending because the Examiner has not demonstrated that Zanetti discloses *a pharmaceutical composition that induces tolerance to an antigen*, said toelrogenic composition comprising a *non-tumor* lymphoid or hematopoietic cell suitable for introduction into an individual and *a pharmaceutically acceptable excipient*, wherein said cell contains a nucleic acid sequence encoding a fusion protein operably linked to a promoter, said fusion protein comprising (1) an immunoglobulin heavy chain or light chain; and (2) a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced; *wherein said composition induces tolerance to the antigen in an individual.*

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[5] Applicants respectfully note that the Office Action cites Zanetti, U.S. Patent No. 5,508,386 (the '386 patent) in the rejection, but also references Zanetti, U.S. Patent No. 5,583,202 (the '202 patent), in the text of the rejection. The Office Action describes the '202 patent as the parent of the '386 patent, and appears to cite claims and column and line numbers from the '202 patent in the rejection (instead of from the cited '386 patent). Applicants note that the '202 patent is not the parent of the '386 patent; instead the applications are both continuations of Application Serial No. 07/947,521. Thus, the two Zanetti patents have the same specification, but different claims.

Zanetti discloses tumor cells, and thus cannot anticipate the present claims

First, the presently pending claims recite "a non-tumor lymphoid or hematopoietic cell" By contrast, Zanetti does not disclose a non-tumor cell. As acknowledged by the Examiner in the Office Action (at page 9), the J558L cells of Zanetti are tumor cells, specifically, myeloma tumor cells. *See also* specification at page 36, lines 17-18 (stating that J558L cells are myeloma cells). Accordingly, Zanetti cannot anticipate the present claims which recite non-tumor lyphoid or hematopoietic cells. Withdrawal of this rejection is respectfully requested.

Moreover, the Examiner did not state in the Office Action that Zanetti disclosed a pharmaceutical composition comprising the cells and a pharmaceutically acceptable excipient as previously or presently claimed. Applicants note that in the Office Action, the Examiner relied only on the teaching of vectors, host cells transfected with the vector, and the description in the specification of various exemplary antigens. *See* Office Action at 9. Accordingly, the Examiner has not made a prima facie case, and withdrawal of this rejection is respectfully requested.

Zanetti cannot anticipate the present claims, which require induction of tolerance

Applicants further respectfully submit that Zanetti does not disclose a pharmaceutical composition for inducing tolerance comprising cells and a pharmaceutically acceptable excipient as presently claimed. During the interview, the Primary Examiner confirmed that the inclusion of the phrase "wherein said composition induces tolerance to the antigen in an individual" was a positive limitation which has patentable weight.

Zanetti concerns use of immunoglobulins for immunization, not pharmaceutical compositions for inducing tolerance comprising cells as described herein

Applicants submit that the fusion proteins (termed "fusion immunoglobulins") of Zanetti are used as immunogens, not to induce tolerance. The primary focus of the reference is the use of the constructs for *inducing* an immunogenic response, as illustrated in the extensive teachings and data on this point. Indeed it is notable that the only exemplified immunoglobulin provided is

an immunodominant epitope of the malarial plasmodium falciparum circumsporozoite, an epitope to which one would not want to induce tolerance. *See, e.g.*, col. 6, lines 6-12 (summarizing experimental results and concluding that the immunogenic properties of the fusion immunoglobulin were expressed); and col. 10, lines 49-62 (determining that the fusion immunoglobulin induced anti-NANP antibodies, and concluding that the epitope produced by the fusion immunoglobulin mimics the native antigen). There is no disclosure in Zanetti of how one would convert an immunogen to its obverse, a tolerogen.

Moreover, the only teaching in Zanetti of cells is of tumor cells for producing immunoglobulins. *See* col. 3, lines 31-34; see also col. 10, lines 49-58 (describing immunizing rabbits with the fusion immunoglobulin containing the malarial epitope). Applicants note that those immunoglobulin compositions contain adjuvant, and are designed to immunize the animals, not for the induction of tolerance. Similarly description of pharmaceutical compositions within Zanetti is directed to pharmaceutical compositions comprising the immunoglobulin proteins themselves.

Accordingly, it is evident that a *prima facie* case has not been made and withdrawal of this rejection is respectfully requested.

At best, the Examiner has made an improper inherency rejection because Zanetti does not disclose a pharmaceutical composition *comprising a pharmaceutically acceptable excipient and cells as disclosed herein*

At the interview, however, the Examiner noted that Zanetti discloses a transfected J558L myeloma cell line comprising the pH62NANP construct containing the immunodominant epitope of the malarial plasmodium falciparum circumsporozoite, and asserted that this cell line, when present in tissue culture medium, comprises a pharmaceutical composition as claimed in the present case. Applicants believe that the Examiner is referring to the following sentences in Zanetti:

> Transfectoma cells were cultured, subcloned and screened for secretion of the engineered Ig molecule using a sandwich enzyme-linked immunosorbant assay (ELISA) . . . .
>
> (Col. 8, lines 57-59)

and

> The pNy1NANP construct was electroporated into J558L cells and subsequently cultured in the presence of G418.
>
> (Col. 8, lines 29-31).

The teaching noted by the Examiner does not disclose a pharmaceutically acceptable excipient, or indeed, any specific medium *at all*

Applicants note that these excerpts do not describe a particular tissue culture medium, or even state that cells were cultured in tissue culture medium, as opposed to culture on a solid or semi-solid surface, such as tissue culture plates. These excerpts (and the rest of Zanetti) also fail to describe that the tumor cell are present in a pharmaceutical composition that further comprises a pharmaceutically acceptable excipient.

The Examiner's statement is based on an alleged inherent disclosure of a pharmaceutically acceptable excipient.

Applicants submit that the Examiner's assertion that the transfected tumor cells in culture anticipate the present (and previously pending) claims directed to pharmaceutical compositions comprising non-tumor cells and pharmaceutically acceptable excipient, constitutes a rejection based on alleged inherent anticipation, because Zanetti is silent about the presence of a pharmaceutically acceptable excipient (and indeed, about the precise identity of the tissue culture medium, or that tissue culture medium was used at all). Accordingly, the characteristics relied upon by the Examiner in this assertion-- that the transfectoma cells are present in a tissue culture medium that allegedly constitutes a pharmaceutically acceptable medium-- are at best inherently present in Zanetti, and accordingly, the Examiner must demonstrate that these characteristics are inherently present in Zanetti.

The Examiner has not made a prima facie case for inherent anticipation

Applicants respectfully point out that the Examiner has not made a prima facie case for inherent anticipation under 35 U.S.C. § 102, and has not provided the required basis for alleging inherent anticipation. As such, the rejection does not stand and Applicants are not required to present any contrary evidence, as requested by the Examiner in the interview.

The legal standard for inherency

The requirements for a rejection based on inherency are stated in M.P.E.P. § 2112, which describes the Examiner's burden in making such a rejection:

> In relying on the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.
> M.P.E.P. § 2112 (emphasis in original).

Moreover, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." Id. (quoting In re Oelrich, 212 USPQ 323, 326 (CCPA 1981).[6]

The Examiner's burden for making an inherency rejection

Accordingly, in order to make a prima facie case of inherent anticipation based on the cited references, the Examiner is required to advance a basis in fact and/or technical reasoning to reasonably support the assertion that the pharmaceutical composition as presently claimed is necessarily present in the cell culture described in Zanetti.

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[6] The M.P.E.P. is in accordance with well-established case law addressing inherency. To serve as an anticipation when the reference is silent about the asserted inherent characteristic, the missing descriptive matter must be shown to be necessarily present in the thing described in the reference, and that it would be so recognized by the person of ordinary skill in the art. See Continental Can Co. v. Monsanto Co., 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). "Inherency may not be established by probabilities or possibilities," In re Oelrich, 212 USPQ 323, 326 (CCPA 1981), and "occasional results are not inherent." Mehl-Biophile Int'l Corp. v. Milgraum, 52 USPQ2d 1303, 1306 (Fed. Cir. 1999).

The Examiner has not satisfied his burden of demonstrating that the cell culture of Zanetti ***necessarily*** constitutes *a pharmaceutically acceptable excipient, as required by the claims.*

Applicants submit that the Examiner has not provided any basis in fact and/or technical reasoning demonstrating that the cell culture of Zanetti necessarily constitutes a pharmaceutical composition as presently claimed. For example, the Examiner has not even demonstrated (a) that the culture was liquid culture, as opposed to, e.g., culture on a solid or semi-solid surface such as on a plate; or (b) what tissue culture medium was disclosed in Zanetti (if any). The Examiner has certainly not advanced a basis in fact and/or technical reasoning demonstrating that the alleged tissue culture medium constitutes a pharmaceutically acceptable excipient. Thus, the Examiner has not met his burden in making this rejection, and the rejection should be withdrawn.

Tissue culture medium (if present) is not a pharmaceutically acceptable excipient

Applicants further submit that tissue culture medium, if present in the Zanetti cell culture, does not constitute a *pharmaceutically acceptable excipient* for a number of reasons:

- most mammalian tissue culture media contain animal products such as serum. One of ordinary skill would not consider a liquid containing animal products--i.e., serum proteins such as extracellular matrix proteins and growth factors-- to be pharmaceutically acceptable for a number of reasons, including that the proteins are likely to be immunogenic in some hosts, and that animal proteins, especially serum proteins, run the risk of contamination with viral or other pathogens (e.g., bovine spongiform encephalitis, hoof and mouth disease, and other pathogens).
- many tissue culture media contain dyes and other chemicals such as pH indicators which would be potentially allergenic and/or potentially toxic when delivered in a pharmaceutical composition.
- Antibiotics are routinely included in tissue culture media; these chemicals are pharmaceutically active, are generally provided by prescription only, and certainly would not qualify as an "excipient", which by definition, is chemically inert.

Accordingly, Applicants submit that the Zanetti cells cannot anticipate the present claims because tissue culture media is not a pharmaceutically acceptable excipient. Withdrawal of this rejection is respectfully requested.

For the above-stated reasons, withdrawal of this rejection is respectfully requested.

Romet-Lemonne

Claims 52-55 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Romet-Lemonne et al. (U.S. Patent No. 6,258,358, July 10, 2001) ("the '358 patent") as supported by Romet-Lemonne et al. US Patent No. 6,248,332, June 19, 2001) ("the '332 patent").[7] The Office Action cites the '332 patent as "supporting the fusion protein made by genetic engineering". Office Action, page 10. The Office Action further cites the '358 patent as teaching a fusion protein comprising IgG and an antigen, and that the antigen can be an allergen or HIV. Applicants respectfully traverse this rejection.

Claims 52-55 have been canceled. New claims 69-78 are to pharmaceutical compositions that induce tolerance to an antigen, said tolerogenic composition comprising a non-tumor lymphoid or hematopoietic cell suitable for introduction into an individual and a pharmaceutically acceptable excipient, wherein said cell contains a nucleic acid sequence encoding a fusion protein operably linked to a promoter, said fusion protein comprising (1) an immunoglobulin heavy chain or light chain; and (2) a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced; wherein said composition induces tolerance to the antigen in an individual.

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[7] Applicants further note that the Office Action appears to cite a combination of two patents, the '338 and '332 patents, in a 102 rejection. However, Applicants note that the '338 and '332 patents are divisional patents claiming benefit to the same parent application, No. 947, 415, and having the same specification (but different claims). Applicants will treat this rejection as a 102 rejection under either patent alone.

Romet-Lemonne does not anticipate the present claims

Applicants submit that the Romet-Lemonne do not teach a pharmaceutical composition according to the pending claims. By contrast, the disclosure in Romet-Lemonne largely concerns so-called "bi-specific binding agents" which are made of two antibodies or fragments thereof, and do not include polypeptides encoding antigens. *See* '202 patent, Col. 5, lines 11-15; Examples 1-4. The only disclosure of a fusion protein comprising an immunoglobulin and an antigen is as follows:

> Alternatively, a fusion protein may be produced by the expression of an immunoglobulin gene genetically engineered to include a gene encoding the antigen (Zanetti (1992) Nature 35:476-477). Such method are described in detail in Sambrook et al. (Molecular Cloning, A laboratory Manual (Second Edition), (Cold Spring Harbor Press, 1989), herein incorporated by reference.
>
> '358 patent, col. 6, line 66- Col. 7, line 5 (cited by the Office Action, page 10); "332 patent (same).

This disclosure does not pertain to pharmaceutical compositions comprising a pharmaceutically acceptable excipient and cells comprising a fusion protein as presently claimed. Nor does Romet-Lemonne disclose pharmaceutical compositions comprising cells expressing such fusion proteins. Indeed, the Examples of Romet-Lemonne exemplify only bi-specific binding agents, which are made in vitro by chemically connecting two antigen binding fragments. No examples disclose fusion proteins (let alone cells comprising fusion proteins). Accordingly, Applicants submit that the Romet-Lemonne patents cannot anticipate the present claims. Prompt withdrawal of this rejection is respectfully requested.

Zambidis

Claims 52-55, 58, 59, 61, and 65-68 are rejected under 35 USC Section 102(b) as allegedly anticipated by Zambidis of record (J. Cell. Biochem. (1993) 9(17)B:251). The examiner states that "[t]he constructs used for electroporation are in a pharmaceutically

acceptable excipient" and that J588L is a myeloma cell line which is a bone marrow tumor cell line. Office Action, page 11. Applicants respectfully traverse this rejection.

Applicants note that claims 52-68 have been canceled. Applicants will address the rejection in the context of pending claims 69-78, to the extent that the rejection may be deemed to so apply.

The Examiner has not made a prima facie case of anticipation

For a cited reference to anticipate a claimed invention, the reference must disclose each and every element of the claimed invention. The Examiner has not made a *prima facie* case that Zambidis anticipates the claims as presently pending because the Examiner has not demonstrated that Zambidis discloses *a pharmaceutical composition that induces tolerance* to an antigen, said pharmaceutical composition comprising *a pharmaceutically acceptable excipient* and a *non-tumor* lymphoid or hematopoietic cell suitable for introduction into an individual, said cell containing a nucleic acid sequence encoding a fusion protein operably linked to a promoter, said fusion protein comprising a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced as presently claimed.

Applicants note that in the Office Action, the Examiner notes only that "the constructs used for electroporation are in a pharmaceutically acceptable buffer" and that J588L cells are myeloma cell lines. Office Acton, page 11. Applicants believe that the Examiner is referring to the following sentences in Zambidis:

> These H chain constructs have been electroporated into J558L cells and recombinant molecules have been purified from transfectoma supernantants and analyzed.
>
> Zambidis at lines 16-19.

Zambidis discloses tumor cells and does not teach or suggest non-tumor cells

A prima facie case of anticipation has not been made because Zambidis does not disclose a non-tumor cell. By contrast (and as acknowledged by the Examiner in the rejection), the J558L

cells disclosed in Zambidis are tumor cells, specifically, myeloma tumor cells. *See also* specification at page 36, lines 17-18 (stating that J558L cells are myeloma cells). Accordingly, Zambidis cannot anticipate the present claims which recite non-tumor lymphoid or hematopoietic cells. Withdrawal of this rejection is respectfully requested.

The teaching noted by the Examiner *do not disclose a pharmaceutical composition for inducing tolerance comprising a pharmaceutically acceptable excipient and cells as presently claimed*

Applicants note that Zambidis at lines 16-18 (quoted above) merely states that a construct was electroporated into a cell line, and does not disclose a pharmaceutical composition comprising cells and a pharmaceutically acceptable excipient as presently claimed. The only cells disclosed in Zambidis are J558 myeloma cells that have been electroporated. There is no description of the particular electroporation buffer, or that the cells present in the electroporation buffer comprise a cell containing a nucleic acid sequence encoding a fusion protein operably linked to a promoter, said fusion protein comprising a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced as presently claimed. Zambidis largely concerns the fusion peptides themselves, and there is no reference to any cells other than the sentence quoted above.

Accordingly, Applicants submit that a *prima facie* case of anticipation has not been made. Withdrawal of this rejection is respectfully requested.

Zambidis can not anticipate the present claims, which require induction of tolerance

Applicants further respectfully submit that Zambidis does not disclose a pharmaceutical composition for inducing tolerance comprising cells and a pharmaceutically acceptable excipient as presently claimed. During the interview, the Primary Examiner confirmed that the inclusion of the phrase "wherein said composition induces tolerance to the antigen in an individual" was a positive limitation which has patentable weight.

Zambidis concerns use of cells for producing immunoglobulins, not pharmaceutical compositions for inducing tolerance comprising cells as described herein

Applicants respectfully point out that Zambidis concerns the construction and production of fusion immunoglobulins, and the only disclosure of cells is in the context of the use of tumor cells to produce fusion immunoglobulin. *See* lines 18-21, quoted above, which constitute the only reference to cells in Zambidis. Thus, the tumor cells of Zambidis are merely used to produce a fusion immunoglobulin product for further analysis.

At most, Zambidis contains a suggestion to use immunoglobulins to induce tolerance; however, Zambidis makes no mention of the use of cells to induce tolerance

Zambidis does not disclose or even suggest using a pharmaceutical composition for inducing tolerance, wherein said composition induces tolerance to the antigen in an individual. Although the abstract mentions the general purpose of making the fusion immunoglobulins--to induce tolerance to the immunoglobulin-- the abstract does not provide any teachings of tolerance induction, but is merely an invitation to experiment with the fusion immunoglobulins.

By contrast, the present claims recite a pharmaceutical composition comprising non-tumor lymphoid or hematopoietic *cells* and a pharmaceutically acceptable excipient. Zambidis, however, makes no reference to pharmaceutical compositions for inducing tolerance comprising a pharmaceutically acceptable excipient and the non-tumor cells as presently claimed. As noted above, the only mention of cells is one sentence that describes production of immunoglobulins in tumor cells. Accordingly, it is evident that Zambidis does not even contain a suggestion to use pharmaceutical compositions comprising a pharmaceutically acceptable excipient and non-tumor cells as presently claimed for the induction of tolerance. Thus, Zambidis can not anticipate the present claims, and withdrawal of this rejection is respectfully requested.

The rejection is improperly based on an alleged inherent disclosure of a pharmaceutically acceptable excipient.

Applicants submit that the Examiner's assertion that the "the constructs used for electroporation are in a pharmaceutically acceptable buffer" and that J588L cells are myeloma

cell lines at best constitutes a rejection based on alleged inherent anticipation, because Zambidis is silent about the presence of a pharmaceutically acceptable excipient (and indeed, about the precise identity of electroporation buffer or indeed, the presence of cells as presently claimed in the electroporation buffer). Accordingly, the characteristics relied upon by the Examiner in this assertion-- that the constructs used for electroporation are in a pharmaceutically acceptable buffer" and (presumably) that the cells as presently claimed are present in the electroporation buffer-- are at best inherently present in Zambidis, and accordingly, the Examiner must demonstrate that these characteristics are inherently present in Zambidis.

The Examiner has not made a prima facie case of inherent anticipation

Applicants respectfully point out that the Examiner has not made a prima facie case for inherent anticipation under 35 U.S.C. § 102, and has not provided the required basis for alleging inherent anticipation. The legal standard for inherent anticipation is described above. Applicants submit that the Examiner has not provided any basis in fact and/or technical reasoning demonstrating that the electroporation mixtures of Zambidis constitute a pharmaceutical composition as presently claimed. Thus, the Examiner has not met his burden in making this rejection, and the rejection should be withdrawn. As such, the rejection does not stand and Applicants are not required to present any contrary evidence, as requested by the Examiner in the interview.

Electroporation buffer does not constitute a pharmaceutically acceptable excipient

Even so, Applicants further submit that electroporation buffer does not constitute a pharmaceutically acceptable excipient for a number of reasons:

- many electroporation buffer are hypoosmolar in order to facilitate electroporation by expanding cell volume prior to delivery of the electric pulse. One skilled in the art would not consider cell expansion due to hyperosmarity to be a desirable feature of a pharmaceutical excipient because:

- delivery of a hypoosmotic composition to a host would prove undesirable under certain circumstances, e.g., IV delivery.
- hypoosmolarity can cause cell death in some cell types.

Accordingly, Applicants submit that Zambidis cannot anticipate the pending claims. Withdrawal of this rejection is respectfully requested.[8]

Rejections under 35 U.S.C. § 103

Zanetti, in view of recited GenBank Record Nos.

Claims 52-55, 58 and 62-68 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zanetti (US Patent No. 5,508,386, April 16, 1996) in view of GenBank Record No. gi:485370; gi:169626; gi:166436; gi:387591; gi:217305; gi:182802; 32323; gi:30101; gi:187400; gi:37173; gi:88229; gi:529041 or gi:575493. Applicants respectfully traverse this rejection.

Applicants note that claims 52-68 have been canceled. Applicants will address the rejection in the context of pending claims 69-78, to the extent that the rejection may be deemed to so apply. Applicants further point out the present claims do not recite the particular peptides disclosed in the cited GenBank listings.

A prima facie case of obviousness has not been made

Applicants respectfully submit that the Examiner has not made a prima facie case of obviousness under Section 103. To establish a prima facie case of obviousness, three basic criteria must be met. First, the prior art reference(s) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation to modify the reference or to

---

[8] For the record, Applicants disagree with the Office Action's statement that "pharmaceutical composition", "suitable for introduction into an individual" and "syngeneic" are intended uses, and do not bear patentable weight. Applicants submit that these terms are describe inherent characteristics of the claimed invention and as such, bear patentable weight.

combine reference teaching. Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

Applicants submit that the references do not teach or suggest each and every of the claim limitation. As noted above, the Examiner has not made a prima facie case that Zanetti inherently discloses the claimed pharmaceutical composition comprising a pharmaceutically acceptable excipient and a non-tumor lymphoid or hematopoietic cell suitable for introduction into an individual, said cell containing a nucleic acid sequence encoding a fusion protein operably linked to a promoter, said fusion protein comprising a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced.

The cited GenBank sequences do not cure this deficiency: the GenBank accession numbers merely recite the DNA sequence of selected antigens or antigenic polypeptides. Moreover, the present claims do not even recite the particular peptides disclosed in the Gen Bank listings. Because each and every element of the claims is not taught or suggested by the cited references, a *prima facie* case of obviousness is not made.

Finally, Applicants assert that reliance on inherency is an improper legal standard for obviousness. In *In re Rijckaert*, the Federal Circuit reversed an obviousness rejection based on the combination of two prior art rejections, where one of the limitations was allegedly inherently taught by one of the references. *See In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). The court held that a *prima facie* case of obviousness had not been established because "[t]hat that is inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *Id.* (citations omitted); *see also In re Spormann,* 150 USPQ 449, 452 (CCPA 1966). Accordingly, inherent disclosure in a cited reference may not be relied upon in making a *prima facie* case of obviousness under Section 103.

Zambidis, in view of Zanetti and Chambers

Claims 52, 55-59, 61, 65-68 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zambidis (Feb. 1, 1993, J. Cellular Biochem, Vol. 9, No. 17, Part B, page 251) in view of Zanetti (Jan. 30, 1992, Nature, Vol. 355, pages 476-477) ("Zanetti *Nature* article") and Chambers (Feb. 1992, PNAS, USA, Vol. 89, pages 1026-1030).[9] Applicants respectfully traverse this rejection.

Applicants note that claims 52-68 have been canceled. Applicants will address the rejection in the context of pending claims 69-78, to the extent that the rejection may be deemed to so apply.

A prima facie case of obviousness has not been made

Applicants respectfully submit that the Examiner has not made a prima facie case of obviousness under Section 103. To establish a prima facie case of obviousness, three basic criteria must be met. First, the prior art reference(s) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation to modify the reference or to combine reference teaching. Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

Applicants submit that the references do not teach or suggest each and every of the claim limitation. As discussed under the §102 rejection above, Zambidis et al. does not teach all the limitations of the claimed invention.

Chambers and Zanetti do not cure this deficiency. The Chambers reference is directed to expressing lymphokines in peripheral blood lymphocytes (PBL) using a retroviral construct encoding the b-actin promoter/enhancer, and the Zanetti reference is directed to construction of immunoglobulin molecules that are able to localize on certain cell/receptor sites and elicit reactivity to antigens specific for an introduced novel antigenic determinant or epitope. Neither

[9] Applicants note for the record that it is not nor has it ever been Applicant's position that Zanetti and Chambers are allegedly non-analogous art, as asserted by the Examiner. Office Action, page 13.

reference teaches or suggests a pharmaceutical composition *that induces tolerance* to an antigen, said pharmaceutical composition comprising *a pharmaceutically acceptable excipient* and a *non-tumor* lymphoid or hematopoietic cell suitable for introduction into an individual, said cell containing a nucleic acid sequence encoding a fusion protein operably linked to a promoter, said fusion protein comprising a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced as presently claimed.

Because the cited references do not teach or suggest all of the elements of the claims, a *prima facie* case of obviousness has not been made. Prompt withdrawal of this rejection is respectfully requested.

Moreover, Applicants note that reliance on inherency is an improper legal standard for obviousness. In *In re Rijckaert*, the Federal Circuit reversed an obviousness rejection based on the combination of two prior art rejections, where one of the limitations was allegedly inherently taught by one of the references. *See In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). The court held that a *prima facie* case of obviousness had not been established because "[t]hat that is inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *Id.* (citations omitted); *see also In re Spormann,* 150 USPQ 449, 452 (CCPA 1966). Accordingly, inherent disclosure in a cited reference may not be relied upon in making a *prima facie* case of obviousness under Section 103.

CONCLUSION

In light of the Amendments and the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the fee transmittal is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 308072000110.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph starting on page 4, line 16 with the following:

[FIGURE 1] FIGURE 1A and 1B: Strategy for preparation of a murine DNA construct coding for a fusion immunoglobulin including the 12-26 epitope of λ-CI repressor protein at the N-terminus of IgG1: (A) A map of plasmid pSNR containing the genomic sequence for a γ1 H chain, modified as descried in Example 1. (B) Restriction map and sequence showing the DNA sequence coding for the 12-26 epitope as combined with the DNA sequence coding for the variable region of the heavy chain (SEQ ID NO:9, SEQ ID NO:10).

Please replace the paragraphs starting on page 31, line 32 and ending on line 33 with the following:

5′ CTG GAG GAC GCG CGG CGG CTG AAG GCG ATA TAC GAG AAG AAG AAG 3′

(SEQ ID NO:1)

3′ GAC CTC CTG CGC GCC GCC GAC TTC CGC TAT ATG CTC TTC TTC CCT 5′

(SEQ ID NO:11)

Please replace the paragraphs starting on page 35, line 7 and ending on line 12 with the following:

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CAG GTC CAA CTG CAG CTG GAG GAC GCG CGG CGG CTG AAG GCG
            L   E   D   A   R   R   L   K   A

ATA TAC GAG AAG AAG AAG CAG GTC CAA CTG CAG (SEQ ID NO:5)
I   Y   E   K   K   K (SEQ ID NO:2)
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Client Reference ARC 088 DIV1